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13. ABSTRACT (Maximum 200 Words)

Purpose: Purpose was to develop non-invasive imaging systems to detect and treatment monitoring of breast cancer at the earliest stage in animal model.

Scope: Scope of the second year's research is to perform in vitro and in vivo experiments, development of stable cell lines producing light-based reporters, development of additional viral vectors encoding dual reporter system, such as light based reporter (GFP, luciferase) and gamma camera based reporter (hSSTR2). Continue *in vivo* imaging in animal models with vector administration.

Major findings: (1) Gamma camera imaging validated the newly developed light-based imaging. (2) Non-palpable breast tumor cells implanted in nude mice were detected non-invasively by light-based (bioluminescence) imaging. (3) Developed a novel technology to produce breast cancer cell lines that stably express GFP or luciferase. (4) Effects of adriamycin on breast cancer xenografts were detected non-invasively. (5) New vectors (Ad-GFP-hSSTr2-TK) were developed for further study on *in vivo* imaging. (6) Complement was found to play a major role in the delivery of vector to host and vector-host relation.

Results: Normal looking non-palpable early stage breast cancer cells were detected and identified in animal models by light-based imaging. Results are presented and submitted for publication (please see the attachment).

Significance: The present studies are highly significant for pre-clinical investigation on the early detection and treatment monitoring of breast cancer xenografts. This technology could be useful to assess the efficacy of new drugs against breast cancer in animal models. Complement plays a major role in response to viral vector administration into the host.

14. SUBJECT TERMS

Breast cancer, light-based imaging, gamma camera imaging, non-invasive, spatial resolution, visualization of breast cancer cells, radiotracer uptake

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Table of Contents

Introduction:

The ultimate goal of the present proposal is to apply novel technology of imaging to detect early stage breast cancer and monitor effects of anti-cancer agents against breast cancer in a non-invasive way in animal model. To accomplish our goals, a combination of multi-modality light-based imaging and gamma camera imaging was proposed. These imaging methods are complementary to each other. Light-based imaging provides high sensitivity and spatial resolution, including the potential for visualization of individual cells and subcellular structures. Light-based imaging technology is complementary to gamma camera imaging by providing molecular imaging of specific receptors and therapies in breast cancer.

Hypothesis: The hypothesis of the proposal was that a combined approach of light-based and gamma camera imaging will improve non-invasive early detection and monitoring of breast cancer.

The following Specific Aims are proposed to test the hypothesis:
1. Conduct *in vitro* studies to optimize strategies for imaging breast cancer using combined light-based imaging and gamma camera imaging.
2. Validate dual-modality imaging in animal models of breast cancer.
3. Apply dual-modality imaging to monitor therapeutic response in animal models of breast cancer.

In the first year, we reported that we successfully accomplished specific aim #1. In addition, we reported that parts of specific aims 2 and 3 were accomplished as well. In the present report we describe the accomplishments of tasks for second year and part of third year. In the following section the accomplishments are described.

Body: For second year parts of Task 2 and 3 were proposed. These tasks deal with the validation of dual-modality imaging in animal models of breast cancer and Apply dual-modality imaging to monitor therapeutic response in animal models of breast cancer. Following areas are covered.

Statement of Work proposed and approved by DOD.

Tasks 1. Conduct *in vitro* studies to optimize strategies for imaging breast cancer using combined light-based imaging and gamma camera imaging

a. Development of new vectors. These are RGD-Ad-GFP (and RFP)-hSSTR2-TK, RGD-Ad-GFP (and RFP)-hSSTR2-CD, Ad-GFP-hSSTR2-TK, Ad-GFP-hSSTR2-CD and retroviral vector encoding GFP and stable transfectants with red fluorescence protein (RFP) or luciferase- (1^{st}, 2^{nd} and 3^{rd} year).

Accomplishment: In the past year we have developed additional adenoviral vectors, Ad-GFP-hSSTR2-TK. These vectors are encoded for GFP and hSSTR2-TK.

Stable GFP and luciferase-positive breast cancer cell lines were developed. Human breast cancer cell line 2LMP, A subclone of MB-MDA231 was used to develop stably GFP and luciferase-positive cells. Luciferase is more sensitive than GFP. We developed a novel method to produce stably GFP or luciferase-positive breast cancer cells.

Task 2. Validate dual-modality imaging in animal models of breast cancer.

a. Implant human breast tumor cells (variable cell numbers - range between 100 cells and 1 million cells) transfected with Ad-GFP-hSSTR2 and newly developed vectors from Task #1 in nude mouse subcutaneously and mammary fat pad to determine how early and what minimum cell numbers can be visualized in live mice. Fluorescence stereomicroscopy will determine the high resolution of GFP and gamma camera imaging will provide the high quantitative analysis of Tc-99m-labeled-P2045 bound to hSSTR2 on tumor cells.(2^{nd} and 3^{rd} year).

Accomplishment:

It was found that light-based imaging (stereomicroscopic and bioluminescence) was more sensitive and had higher resolution than gamma camera imaging. However, for imaging deeper tissue, nuclear imaging using Tc-99m-labeled-P2045 was necessary. A full range of imaging was performed using luciferase-positive human breast cancer cells. For in vivo imaging, a variable number of cells were implanted subcutaneously and in the mammary fat pad. Luciferase imaging was more sensitive than gamma camera imaging for detection of a minimum number of breast cancer cells that were implanted subcutaneously and in the mammary fat pad.

b. Implant subcutaneously and in mammary fat pad breast tumor cells first in athymic nude mice followed by transfection with adenoviral vectors. Perform dual modality imaging. (2^{nd} and 3^{rd} year).

Accomplishment: Effective administration of for in vivo transfection of breast cancer cells by adenoviral vector is a very critical area in the gene therapy studies. Intravenous administration of Ad vector faces several obstacles. Complement is one of the major components. The effect of complement on transgene expression was evaluated *in vivo* and *in vitro* using mice lacking complement components. Complement component 3 (C3) deficient mice ($C3^{-/-}$) and appropriate wild type controls were intravenously injected with a replication incompetent, luciferase-expressing normal Ad5 (Ad5Luc1), or fibritin-fiber Ad5 (Ad5FFLuc1). Repeated, non-invasive bioluminescence imaging was conducted over 35 days. Our data shows for the first time that C3 facilitates both short- and long-term hepatic expression of luciferase following systemic delivery. $C3^{-/-}$ mice showed significantly less ($p<0.05$) luciferase expression in their liver than treatment-matched wild type mice when 2.3×10^9 (Ad5Luc1) and 4.0×10^9 (Ad5Luc1 or Ad5FFLuc1) viral particles (v.p.) were infused. The maximal difference in luciferase activity between $C3^{-/-}$ and wild type mice was 99-fold difference at 3 days for the 2.3×10^9 v.p. dose (Ad5Luc1), 35-fold at 13 d for the 4.0×10^9 v.p. dose (Ad5Luc1), and 22-fold at 13 days

for the $4.0x10^9$ v.p. dose (Ad5FFLuc1). Preincubation of Ad5Luc1 with wild type, $C1q^{-/-}$, or factor B (FB) deficient mouse sera for 5 min significantly ($p<0.05$) increased transduction of mouse liver cells, as compared to preincubation with $C3^{-/-}$ sera or PBS. These results suggest the classical or alternate complement pathway enhances Ad5 mediated liver transduction. These are significant findings for gene therapy research.

c. Image anti-angiogenesis targeting *in vivo*. Inject intravenously a tracer dosage of anti-angiogenesis antibody DC101, dually labeled with Cy5.5 and Tc-99m, into mice bearing GFP-hSSTR2 labeled breast tumor cells at variable numbers. Collect images with stereomicroscopy to measure GFP at one wavelength, Cy5.5 at near infrared, and radioactivity by gamma camera imaging. Repeat the process at different time interval using the same mice (2^{nd} and 3^{rd} year).

Accomplishment: Breast cancer cells (stably luciferase-positive) cells were subcutaneously implanted in athymic nude mice. Ant-angiogenesis antibody DC101 dually labeled with Cy5.5 and Tc-99m was intravenously injected using tail vein. In a preliminary experiment dual modality imaging showed near infrared was more sensitive that gamma camera imaging to detect a small number of cell on the surface. The studies are in progress

Task 3: Apply dual-modality imaging to monitor therapeutic response in animal models of breast cancer.

a. Perform *in vivo* dual modality imaging of chemotherapy. - Image live mice to visualize the therapeutic intervention of adriamycin, tamoxifen and carboplatin to GFP-hSSTR2 positive breast tumor cells. (2^{nd} and 3^{rd} year). The studies are in progress

Accomplishment: GFP-positive and luciferase-positive breast cancer cells were implanted in the mammary fat pad of athymic female nude mice followed by therapeutic intervention with adriamycin and tamoxifen. Tumor cells/lesions were visualized and detected non-invasively long before any solid tumor was visible or palpable. Light-based imaging showed a great potential for studies the effects of drugs on breast cancer in animal model. The localization of anti-cancer drugs was imaged by fluorescent stereomicroscopy.

b. Perform *in vivo* dual modality imaging of anti-angiogeneis therapy. - Image live mice (implanted with breast tumor cells transfected with Ad-GFP-hSSTR2 before and after implantation) to visualize the effects of dual-labeled (Cy5.5-Tc-99m) anti-angiogenesis antibody DC101 on GFP-positive breast tumor cells (2^{nd} and 3^{rd} year).

Accomplishment: GFP-positive breast cancer cells were implanted in the mammary fat pad of athymic nude mice followed by dual-labeled anti-angiogenesis antibody DC102. Breast tumors were detected using dual modality imaging system. At the same time GFP-positive cells were imaged to visualize the location of tumors in mice. The studies are in progress.

Key Research Accomplishment:

- Non-invasive light-based imaging methods were developed with stereomicroscope and bioluminescence. The work was presented in the annual meeting of American Association for Cancer Research in March, 2004 (Abstract published in - Appendix I).

- Light-based imaging was shown to be highly sensitive to detect disseminated breast cancer in animal model during therapeutic intervention. This work as an abstract was published in American Society of Clinical Oncology - Appendix II).

- Effective administration of for in vivo transfection of breast cancer cells by adenoviral vector is a very critical area in the gene therapy studies. Intravenous administration of Ad vector faces several obstacles. Complement is one of the major components. The effect of complement on transgene expression was evaluated *in vivo* and *in vitro* using mice lacking complement components. (Manuscript accepted in Gene Therapy, 2004).

- Gamma camera imaging validated the newly developed light-based imaging.

- Non-palpable breast tumor cells implanted in nude mice were detected non-invasively by light-based (bioluminescence) imaging.

- Developed a novel technology to produce breast cancer cell lines that stably express GFP or luciferase.

- Effects of adriamycin on breast cancer xenografts were detected non-invasively.

- New vectors (Ad-GFP-hSSTr2-TK) were developed for further study on *in vivo* imaging.

Reportable outcomes:

Manuscript (Accepted): Bioluminescence imaging reveals a significant role for complement in liver transduction following intravenous delivery of adenovirus. Gene Therapy, 2004.

Manuscript in preparation:
Dual modality imaging for the early detection and treatment monitoring of breast cancer in animal model.

A novel method to produce stably GFP-positive and luciferase-positive breast cancer cells.

Chaudhuri TR, Zhihong Cao, Selvarangan Ponnazhagan, Amanda Stargel, Pushpa L Simhadri, Tong Zhou, Albert F. LoBuglio, Donald J. Buchsbaum and Kurt R. Zinn.

Bioluminiscence imaging of non-palpable breast cancer xenografts during treatment with TRA-8, an anti-DR5 antibody and chemotherapy.

Chaudhuri TR, Zhihong Cao, Selvarangan Ponnazhagan, Amanda Stargel, Pushpa L. Simhadri, Tong Zhou, Albert F. LoBuglio, Donald J. Buchsbaum, and Kurt R. Zinn. Detection of disseminated breast cancer growth and treatment response using non-invasive bioluminescence imaging (BI).

Abstracts Presented:

Chaudhuri TR, Zhihong Cao, Selvarangan Ponnazhagan, Amanda Stargel, Pushpa L Simhadri, Tong Zhou, Albert F. LoBuglio, Donald J. Buchsbaum and Kurt R. Zinn. Bioluminiscence imaging of non-palpable breast cancer xenografts during treatment with TRA-8, an anti-DR5 antibody and chemotherapy. AACR. March, 2004, in Orlando Florida.

Chaudhuri TR, Zhihong Cao, Selvarangan Ponnazhagan, Amanda Stargel, Pushpa L. Simhadri, Tong Zhou, Albert F. LoBuglio, Donald J. Buchsbaum, and Kurt R. Zinn. Detection of disseminated breast cancer growth and treatment response using non-invasive bioluminescence imaging (BI). ASCO, June 2004, in New Orleans, Louisiana.

Chaudhuri TR, Viral delivery of light-based reporters for detection and monitoring of disease. Mol Imaging Biol 6(2): 69, 2004. (Invited).

Chaudhuri, TR, V. N. Krasnykh, Z. Cao, A. Stargel, P. L. Simhadri, N. Belousova, K. R. Zinn. Intravenous administration of adenoviral vector detected metastatic breast cancer by bioluminescent imaging in live mice. Journal of International Conference on Gene Therapy of Cancer, December 10-14, 2003, San Diego, California.

Abstracts Published:

Chaudhuri TR, Zhihong Cao, Selvarangan Ponnazhagan, Amanda Stargel, Pushpa L Simhadri, Tong Zhou, Albert F. LoBuglio, Donald J. Buchsbaum and Kurt R. Zinn. Bioluminiscence imaging of non-palpable breast cancer xenografts during treatment with TRA-8, an anti-DR5 antibody and chemotherapy. Proceedings :AACR. March, 2004.

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Development of cell lines: GFP-positive breast cancer cell line (2LMP-GFP). Luciferase-positive breast cancer cell line (2LMP-luc).

Funding applied for based on work supported by this grant: Partial results of the present research helped to apply for additional funding from Sankyo Co. Ltd. to study the efficacy of a newly developed drug against breast cancer. Proposal has been funded.

Personnel supported by this grant:

Dr. Zhihong Cao, Research Associate

Ms. Amanda Stargel, Research assistant
Ms Glorisa Reason, Laboratory technician.

Conclusions: The light-based imaging continues to show great potential in the detection and treatment monitoring of breast cancer in a non-invasive manner. GFP, RFP, Luciferase or Cy 5 has significant contributing factors in this research. The efficacy of fluorescent stereomicroscopy was validated by gamma camera imaging. Both light-based and gamma camera imaging can detect the breast cancer in animal. However, a contrast such as GFP, RFP is necessary to identify few cancer cells behind millions of normal cells. This is true in vitro as well as in vivo system.
The present studies are highly significant for pre-clinical investigation on the early detection and treatment monitoring of breast cancer xenografts. This technology could be useful to assess the efficacy of new drugs against breast cancer in animal models. Complement plays a major role in response to viral vector administration into the host.

References: Publications and Abstracts:

Kurt R. Zinn, Alexander J. Szalai, Amanda Stargel, Victor Krasnykh, **Tandra R. Chaudhuri**. Bioluminescence imaging reveals a significant role for complement in liver transduction following intravenous delivery of adenovirus. Accepted. Gene Therapy, 2004.

Chaudhuri TR, Zhihong Cao, Selvarangan Ponnazhagan, Amanda Stargel, Pushpa L Simhadri, Tong Zhou, Albert F. LoBuglio, Donald J. Buchsbaum and Kurt R. Zinn. Bioluminiscence imaging of non-palpable breast cancer xenografts during treatment with TRA-8, an anti-DR5 antibody and chemotherapy. Proceedings :AACR. March, 2004.

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Appendices:

Appendix I: Chaudhuri TR, Zhihong Cao, Selvarangan Ponnazhagan, Amanda Stargel, Pushpa L Simhadri, Tong Zhou, Albert F. LoBuglio, Donald J. Buchsbaum and Kurt R. Zinn. Bioluminiscence imaging of non-palpable breast cancer xenografts during treatment with TRA-8, an anti-DR5 antibody and chemotherapy. Proceedings:AACR. March, 2004.

Appendix II: Chaudhuri TR, Zhihong Cao, Selvarangan Ponnazhagan, Amanda Stargel, Pushpa L. Simhadri, Tong Zhou, Albert F. LoBuglio, Donald J. Buchsbaum, and Kurt R. Zinn. Detection of disseminated breast cancer growth and treatment response using non-invasive bioluminescence imaging (BI). Proceedings: ASCO, June 2004.

Appendix III: Kurt R. Zinn, Alexander J. Szalai, Amanda Stargel, Victor Krasnykh, **Tandra R. Chaudhuri**. Bioluminescence imaging reveals a significant role for complement in liver transduction following intravenous delivery of adenovirus. Accepted. Gene Therapy, 2004.

Appendix IV:

CV – Dr. Tandra Rani Chaudhuri.

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American Association for Cancer Research

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Bioluminescence imaging of non-palpable breast cancer xenografts during treatment with TRA-8, an anti-DR5 antibody and chemotherapy

Tandra R. Chaudhuri, Zhihong Cao, Selvarangan Ponnazhagan, Amanda Stargel, Pushpa L. Simhadri, Tong Zhou, Albert F. LoBuglio, Donald J. Buchsbaum, Kurt R. Zinn. University of Alabama at Birmingham, Birmingham, AL

Background
While TRA-8, an anti-DR5 antibody, induces apoptosis in TRAIL-sensitive tumor cells, no sensitive non-invasive methods are available to monitor the treatment effects on minimal disease in animal models. Bioluminescence imaging allows quantitative assessment of a small number of cells, and monitoring the tumor growth and treatment response by detecting the light emitted from tumor cells expressing the firefly luciferase (Luc) as a reporter gene. We report our non-invasive monitoring of multimodality treatments against non-palpable breast cancer xenografts in live animals.
Aim
The purpose of the study was to apply bioluminescence imaging to detect treatment effects in non-palpable breast tumors in mice. TRA-8 antibody and Adriamycin were tested alone, or in combination.
Methods
To accomplish our goals, the human breast tumor cell line 2LMP (a subclone of MDA-MB231 obtained from M. Lippman, Univ. of Michigan) was transfected with adeno-associated virus encoding firefly Luc gene, and a stable Luc-positive 2LMP (Luc-2LMP) cell line was established by screening clones in 96-well plates using a Xenogen IVIS-100 imaging system. In vitro studies established that the Luc-2LMP cell line responded identically to treatments, as compared to the parent cell line. For in vivo studies, four groups (4/group) of athymic female nude mice were implanted with Luc-2LMP cells (1 million/mouse) in the mammary fat pad. Treatments included combined TRA-8 (100-200 microgram/mouse)/Adriamycin (6 mg/kg) (Gr 1), TRA-8 (Gr 2), Adriamycin (Gr 3), and untreated controls (Gr 4). All treatments were given intravenously (2X/week for 4 wks). Mice were imaged over time with the IVIS-100, and tumor mass was determined by measuring light transmitted from the Luc-positive tumors.
Results
Bioluminescence imaging demonstrated high sensitivity for non-invasive detection and treatment monitoring of non-palpable breast tumors in mice. The measurement of light emission from stable Luc-2LMP cells in mice allowed tracking the tumor regression during therapy. Real time imaging data revealed significant inhibition of tumor growth in all treatment groups relative to controls, while the combined treatment with TRA-8/Adriamycin was most effective. ~ 95% of tumor cells were killed after the first two doses of combination therapy.

Conclusions
Bioluminescence imaging was applied to evaluate a combined TRA-8/Adriamycin strategy for apopotosis induction in breast cancer xenografts. This method can be more widely applied for new drugs and combinations for cancer therapy, enabling non-invasive assessment of tumor cell killing over time. (Supported in part by Sankyo Co., Ltd, DAMD17-02-1-0264, and DAMD17-02-1-0266, NIH grant # CA80104.)
Author Disclosure Block: T.R. Chaudhuri, None; **Z. Cao**, None; **S. Ponnazhagan**, None; **A. Stargel**, None; **P.L. Simhadri**, None; **T. Zhou**, None; **A.F. LoBuglio**, None; **D.J. Buchsbaum**, None; **K.R. Zinn**, None.

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Accepted to be published in American Society of Clinical Oncology, June, 2004, New Orleans, Louisiana.

Detection of disseminated breast cancer growth and treatment response using non-invasive bioluminescence imaging

T. R. Chaudhuri, Z. Cao, S. Ponnazhagan, A. Stargel, P. L. Simhadri, T. Zhou, A. F. LoBuglio, D. J. Buchsbaum, K. R. Zinn; University of Alabama at Birmingham, Birmingham, AL

Background: TRA-8, a mouse anti-human DR5 monoclonal antibody induces apoptosis in TRAIL-sensitive tumor cells. However no non-invasive method is available to monitor the treatment effects on disseminated cancer. We report a non-invasive and sensitive BI technology to determine the efficacy of combined treatment of TRA-8 and Adriamycin on disseminated breast cancer in animal model. **Methods**: Human breast cancer cell line 2LMP, a subclone of MDA-MB-231, was transfected with adeno associated virus encoding luciferase (AAV-luc). A stable luciferase-positive cell line was established by screening. Two groups (5/group) of athymic female nude mice were used. Four sites (liver, spleen, chest cavity and peritoneum) of each mouse were injected with luciferase-positive 2LMP cells (0.25x106/site). After 7 days, BI revealed disseminated tumor sites; one group of mice was injected i.v. with 150 µg TRA-8 and 6 mg/kg Adriamycin, and the 2nd group of mice did not receive any treatment. All treatments were given 2X/wk for 3 wks. Mice were imaged over time with an IVIS-100 Xenogen imaging system and tumor mass was estimated from ventral, dorsal, left and right lateral views by measuring light transmitted from the luciferase positive tumors. **Results:** All untreated mice died by day 21 with 4-6 fold increases in bioluminescence and extensive metastasis, including bone. Treated mice had a dramatic decrease in bioluminescence to 15-20% of day 7 values that persisted for 45 days and then began a progressive regrowth of tumor (increasing bioluminescence) in multiple sites. Dissemination of breast cancer was detected by BI and confirmed by dissection. In all untreated mice, numerous tumor nodules were detected in lungs, heart, pleural space, bones including ribs and spine, diaphragm, esophagus and pericardium, liver, spleen, stomach, kidneys, ovaries, uterus, and peritoneal membrane. **Conclusions**: BI demonstrated high sensitivity for non-invasive detection and treatment monitoring of disseminated breast tumors in mice. Combination therapy with TRA-8 and Adriamycin was highly effective in the regression of disseminated breast cancer in this animal model. (Supported by DAMD17-02-1-0266, NIH CA80104, DAMD17-02-1-0264, Sankyo C0,Ltd.)

Bioluminescence imaging reveals a significant role for complement in liver transduction following intravenous delivery of adenovirus

REVISED #2

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Running Title: Complement and liver transduction by adenovirus

Keywords: luciferase, adenovirus, innate immunity, gene therapy, inflammation, complement

Summary

The effect of complement on transgene expression was evaluated *in vivo* and *in vitro* using mice lacking complement components. Complement component 3 (C3) deficient mice ($C3^{-/-}$) and appropriate wildtype controls were intravenously injected with a replication incompetent, luciferase-expressing normal Ad5 (Ad5Luc1), or fibritin-fiber Ad5 (Ad5FFLuc1). Repeated, non-invasive bioluminescence imaging was conducted over 35 days. Our data shows for the first time that C3 facilitates both short- and long-term hepatic expression of luciferase following systemic delivery. $C3^{-/-}$ mice showed significantly less ($p<0.05$) luciferase expression in their liver than treatment-matched wildtype mice when 2.3 $x10^9$ (Ad5Luc1) and $4.0x10^9$ (Ad5Luc1 or Ad5FFLuc1) viral particles (v.p.) were infused. The maximal difference in luciferase activity between $C3^{-/-}$ and wildtype mice was 99-fold difference at 3 days for the $2.3x10^9$ v.p. dose (Ad5Luc1), 35-fold at 13 d for the $4.0x10^9$ v.p. dose (Ad5Luc1), and 22-fold at 13 days for the $4.0x10^9$ v.p. dose (Ad5FFLuc1). Preincubation of Ad5Luc1 with wild-type, $C1q^{-/-}$, or factor B (FB) deficient mouse sera for 5 min significantly ($p<0.05$) increased transduction of mouse liver cells, as compared to preincubation with $C3^{-/-}$ sera or PBS. These results suggest the classical or alternate complement pathway enhances Ad5 mediated liver transduction.

Activation of innate immunity and promotion of inflammation are common responses to replication incompetent adenoviruses (Ad) now being developed as vectors for gene therapy.[1,2] The complement system is central to both innate immunity and inflammation.[3,4] Because it is comprised of multiple membrane-bound and blood-borne factors, the complement system is probably of particular relevance in delivery of vectors administered intravenously. In fact, Cichon *et al* showed complement was activated in a majority of human plasma samples when challenged with different adenoviral serotypes; complement activation was completely dependent on anti-Ad antibody.[5] Based on these studies, the suggestion was made that complement activation would not be a problem for local delivery of low Ad doses, but high doses of Ad administered by a systemic route could have potentially adverse consequences.[5]

Complement "activation" is a complex series of enzymatic reactions that converts pre-existing protein substrates into biologically active end-products. For example, in a process called opsonization, the deposition of C3 fragments onto pathogens promotes the removal of the pathogens by the reticuloendothelial system. In gene therapy applications, redirection of the vector in this manner might lead to toxicity. Equally important, less vector would remain available for transfecting the desired target cell population. Consistent with this view, Wilson *et al* reported greater reporter expression in mouse hepatocytes following systemic Ad administration with high vector doses that saturated Kupffer cells.[6] This was true even with doses that included a different Ad without the reporter construct.[6]

It is widely accepted that the liver is the predominant site of reporter gene expression following intravenous injection of wild-type Ad5 vectors.[7] Coxsackie and

adenovirus receptor (CAR), integrins, and heparin sulfate proteoglycans have all been shown to be important for liver transfection.[7-12] Ad vectors with CAR binding site mutations and ablation of integrin-binding showed less luciferase expression in liver following systemic administration.[7] Similarly, ablation of CAR-binding via short fiber replacements also lead to reduced liver tropism.[11] More recently it was reported that blood coagulation factor IX was also involved in liver transduction.[13] The humoral immune response also influences liver transgene expression, especially when the host is repeatedly exposed to the vector, because neutralizing antibody can diminish liver transfection.

The data reported herein show for the first time the importance of complement in the transduction of mouse liver by Ad. To directly address the role of complement in liver transduction, we performed studies using wildtype mice versus mutant mice unable to make complement component 3 (C3).[14] By repeated bioluminescence imaging of living mice, we assessed liver luciferase expression following intravenous delivery of the Ad vector. Surprisingly, at low Ad5Luc1 doses, C3 deficient mice ($C3^{-/-}$) showed up to 99-fold less luciferase expression in the liver compared to wildtype controls, indicating a facilitatory role for the complement pathway in liver transduction. The current experiments used $C3^{-/-}$ mice with the C57BL/6 background, together with littermate controls (homozygous $C3^{+/+}$) matched for sex and age (hereafter, wildtype or control).

In Figure 1 we present representative images captured from mice that received the lowest dose ($2.3x10^9$ v.p.) of Ad5Luc1. Each image (1-min acquisition) was collected on day 13 after Ad5Luc1 delivery; the pseudocolor overlay represents the intensity of light emission, and thus the level of luciferase expression. Overall, wildtype

mice showed 12.7-fold greater liver luciferase expression than $C3^{-/-}$ mice at this time point, and the absolute difference was statistically significant ($p<0.05$, ANOVA).[15]

With all 3 doses of Ad5Luc1, peak liver luciferase expression in both kinds of mice was detected on day 6-10 (Fig. 2). Maximal luciferase expression ranged from 10- to 100-times greater than that observed 1-2 d after vector administration. Wildtype mice always showed higher liver luciferase expression, but the absolute difference between wildtype and $C3^{-/-}$ mice was diminished as the dose of Ad5Luc1 was increased. For example, liver luciferase expression 3 days after injection of $2.3x10^9$ v.p. was 99-fold higher in wildtype mice compared to $C3^{-/-}$ mice (Fig. 2A). For mice injected with $4.0x10^9$ v.p. (Fig. 2B), wildtype mice showed 35-fold higher liver luciferase expression compared to $C3^{-/-}$ mice. For the highest Ad5Luc1 dose ($1.3x10^{10}$ v.p.), the maximal difference between the two groups was 3.4-fold (Fig. 2C). For the $C3^{-/-}$ mice in isolation, significantly greater luciferase expression in the liver was observed with increasing Ad5Luc1 vector dose. In contrast, the control mice with an intact complement system did not show greater luciferase expression with increasing Ad5Luc1 dose.

An experiment was performed in the two groups of mice using intravenous Ad5FFLuc1 ($4.0x10^9$ v.p.). Ad5FFLuc1 is a fiber-fibritin Ad5 encoding Luc1 and does not support CAR-dependent pathways of infection.[16] As shown in Figure 3, the wildtype mice averaged higher levels of liver luciferase expression compared with $C3^{-/-}$ mice; maximal difference was 22-fold at 17 days after injection. These data suggest the complement effect on liver transfection is independent of CAR-mediated mechanisms.

Complement appeared to facilitate liver transduction as $C3^{-/-}$ mice always showed lower luciferase expression than wildtype mice. The facilitation effect was overcome if high numbers of the vector were injected, thus $C3^{-/-}$ and wildtype mice showed similar liver luciferase expression after administration of $1.3x10^{10}$ Ad5Luc1. Importantly, none of the mice used in the present study were previously exposed to Ad vectors, so the complement-dependent effect was independent of an antibody response against the Ad vector. Also, the complement-dependent effect did also not require CAR-dependent routes of infection, as demonstrated using Ad5FFLuc1.

Complement activation may lead to opsonization of the vector, binding of the complement-coated vector to cells, and subsequent infection. To test this hypothesis, *in vitro* studies were conducted with Ad5Luc1 and fresh serum from transgenic mice lacking complement components. Mouse liver hepatoma (TIB76) cells were incubated with the Ad5Luc1 following preincubation for 5 min with the various sera. As shown in Figure 4, preincubation of Ad5Luc1 with $C3^{-/-}$ sera resulted in luciferase levels in the TIB76 cells that were not significantly different from levels in TIB76 cells treated with Ad5Luc1 preincubated with PBS. Importantly, preincubation of Ad5Luc1 with $C3^{-/-}$ serum resulted in significantly less ($p<0.05$) luciferase expression (3-fold) compared to preincubation with wildtype serum. Remarkably, preincubation with $C1q^{-/-}$ and $FB^{-/-}$ sera achieved intermediate levels of transduction in the TIB76 cells.

Our *in vitro* and *in vivo* findings suggest that C3, and likely its activation via either a FB- or C1q-dependant pathway, enhances Ad5 mediated transduction of the liver or liver cells. It appears that opsonization of the Ad5 particle itself facilitates transfection, which would point to a potential cellular complement receptor as another important

component of this mechanism. While the current work does not identify this receptor, it provides strong evidence for its existence. Of interest, it was recently reported that group B adenovirus uses CD46, a complement regulatory protein, for cellular attachment.[17] Therefore, the current report provides another example of an adenovirus exploiting a complement pathway for infection. As such, a strong immune response may be a consequence. This is in contrast to other pathways by which pathogens exploit the complement system as a means to escape the host immune response.[18-23] For example, HIV has evolved to exploit complement pathways to survive and promote transmission to permissive cells.[24]

In order for systemic delivery of Ad vectors to achieve clinical practicality, a better understanding of innate immunity is needed, including how complement influences the transduction process. Our findings suggest that inhibition of complement may be a valid approach to overcome the liver's propensity to remove systemically administered Ad, as well as an approach to reduce the strong immune response to the Ad vector. Two reports from another group are supportive of this concept, as complement depletion improved intravascular delivery of replication-conditional Herpes virus to human xenograft tumors growing in rat brain.[25,26] While Ikeda *et al* utilized a different virus and model system, their findings of improved delivery of virus to the brain xenografts following complement inhibition is consistent with reduced opsonization and reduced liver sequestration. Less inactivation and removal of virus would make more available to target the xenograft brain tumors. In addition to benefits for tumor targeting, inhibition of complement activation may also have the added benefit of decreasing the humoral and cell mediated immune response to virus.[27] It is envisioned that future Ad vectors

will display complement regulatory proteins on their surface, or other surface proteins capable of binding negative regulators of complement activation in host blood. Potential sites of incorporation of these proteins in the Ad include the hexon, or pIX, a recently demonstrated site for genetic addition of peptides.[28] A linker site (poly GGGGS) between the FF chimera and retargeting ligands is another potential site.[16] In this manner, negative regulators of complement activation would be present on the surfaces of the Ad vector. Complement activation would thereby be reduced, potentially minimizing undesired toxicities (inflammation, immune response) and/or improving targeting outcomes to tissues other than liver. In combination with other efforts to modify the vector for targeting, efforts to interfere with complement should be considered.

Acknowledgements.

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Figure Legends.

Figure 1: Bioluminescence imaging of luciferase expression in living mice at 13 days after intravenous injection of $2.3x10^9$ v.p. of Ad5Luc1 in (A) wildtype control mice, and (B) $C3^{-/-}$ mice. The pseudocolor overlay represents the intensity of light emission, and thus the level of luciferase expression. A single lot of E1-deleted recombinant Ad5Luc1 containing the firefly luciferase gene under control of CMV promoter was used;[29] all injections of the virus were intravenous. Preliminary studies with a range of

Ad5Luc1 doses ($2x10^9$ - $1x10^{10}$ v.p.) showed from 10- to 100-fold less expression of luciferase in $C3^{-/-}$ mice (4 mice) versus matched controls (4 mice). Based on these initial studies, three additional experiments each with 2 groups of mice each (control and $C3^{-/-}$ mice, n=3-4/group) were conducted to evaluate 3 different Ad5Luc1 doses ($2.3x10^9$, $4.0x10^9$, and $1.3x10^{10}$ v.p.). At various times after administration of Ad5Luc1, the mice were imaged using a bioluminescence imaging system (Xenogen, Inc.) to detect luciferase expression. Images were collected on mice oriented in the same position and always 10 min after intraperitoneal injection of 2.5 mg luciferin. The mice were maintained under enflurane anesthesia at 37 °C, with their ventral surfaces facing the CCD camera that was part of the imaging system. Imaging was performed several times on each mouse, beginning at 6 hr after Ad5Luc1 injection and continuing to day 34. Data acquisition times for imaging ranged from 20 sec to 10 min.

Figure 2: Liver light emission (luciferase expression) over time in the 3 experiments. Mice were intravenously dosed with Ad5Luc1 at (A) 2.3 $x10^9$ v.p./mouse, (B) 4.0 $x10^9$ v.p./mouse, and (C) 1.3 $x10^{10}$ v.p./mouse. The numbers adjacent to the wildtype data points indicate the fold greater expression for the wildtype group relative to the $C3^{-/-}$ group for that time point, with the "*" indicating statistical significance at $p<0.05$. Each line is representative of 4 mice, except there were only 3 control mice in (B). Male mice (A) and female mice (B-C) were used. Light emission from the liver region (relative photons/sec) was measured using software provided by Xenogen, and the intensity represents the liver luciferase activity. This relationship was validated by comparing luciferase measurements from the live animals with independent measurements obtained from tissue homogenates as described.[30] These comparisons

were accomplished at termination by removal of liver and spleen (mice injected with $2.3x10^9$ v.p.), followed by independent *in vitro* luciferase analyses as described. The validation also confirmed that the liver was responsible for >99% of the light emission that was detected in the liver region of the live mice using the Xenogen system.

Figure 3: Liver light emission (luciferase expression) over time in mice intravenously dosed with Ad5FFLuc1 ($4.0 x10^9$ v.p./mouse). The numbers adjacent to the wildtype data points indicate the fold greater expression for the wildtype group relative to the $C3^{-/-}$ group for that time point, with the "*" indicating statistical significance at $p<0.05$. Each line is representative of 5 male mice.

Figure 4: Ad5Luc1-induced luciferase expression in TIB76 cells following treatment with various mouse sera. Ad5Luc1 aliquots (4.0×10^8 v.p., 0.02 ml) were incubated for 5 min (37° C) with 0.1 mL of fresh sera (wildtype, $C1q^{-/-}$, Factor $B^{-/-}$, or $C3^{-/-}$), PBS, or a mixture of wildtype and $C3^{-/-}$ sera. Each mixture was diluted (3 mL) and 0.3 mL was incubated for 1 hr with adherent TIB76 cells in 24-well plates. Luciferase and protein assays were conducted after 22 hrs. Different letters indicate statistically significant differences in treatments at $p<0.05$. These data are from one experiment, but are representative of data from experiments repeated on 3 different days.

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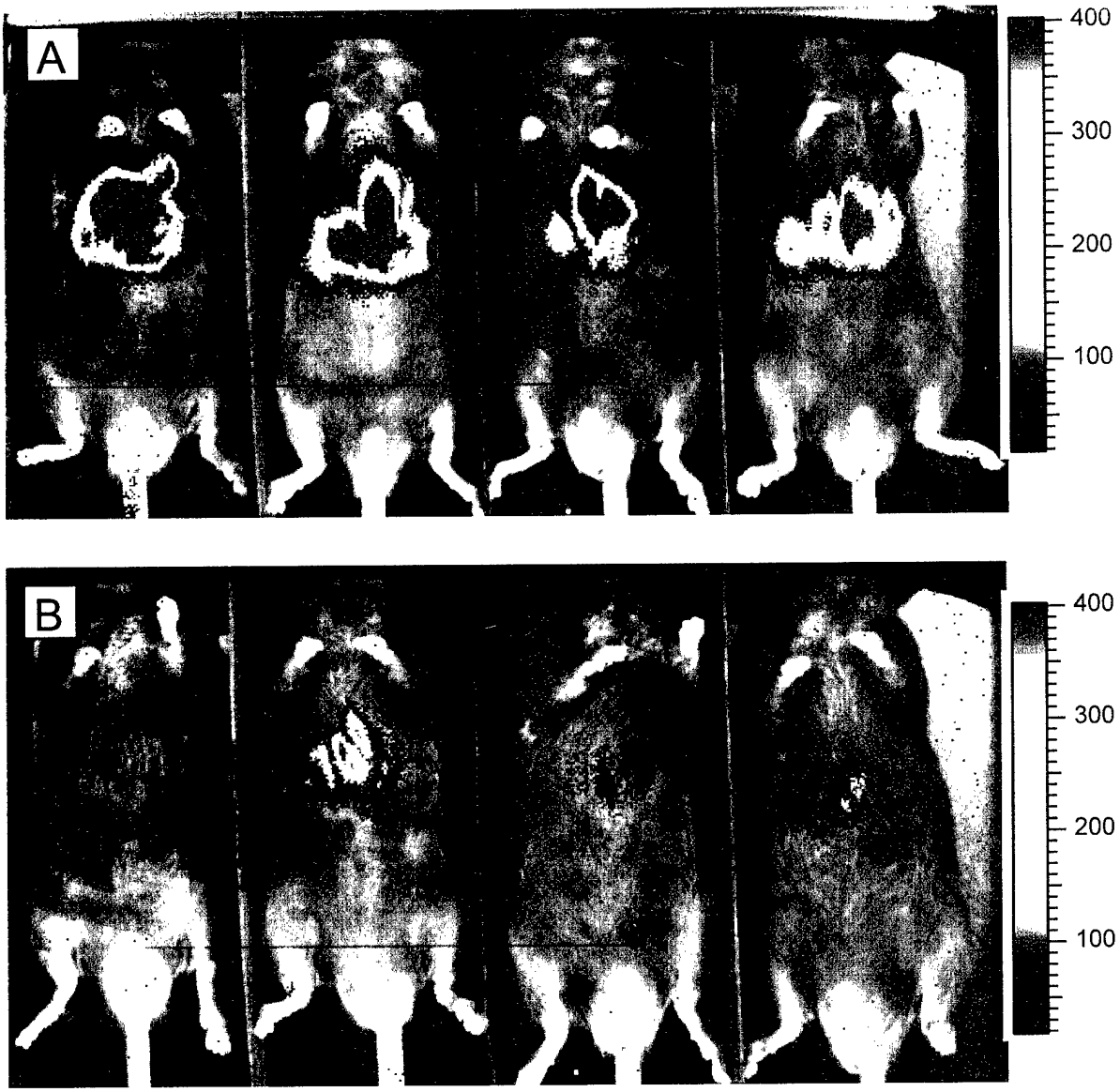
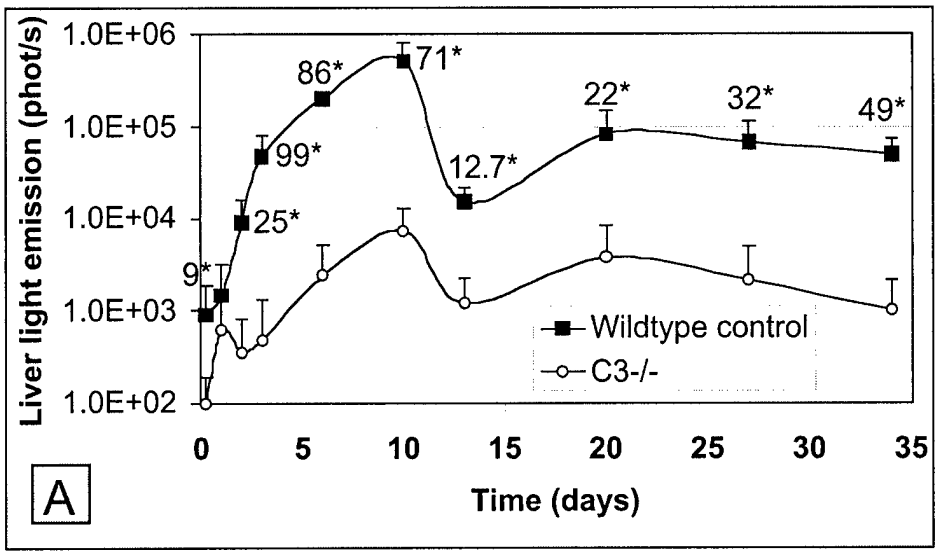


Figure 1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1.0E+04
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9*
25*
99*
86*
71*
12.7*
22*
32*
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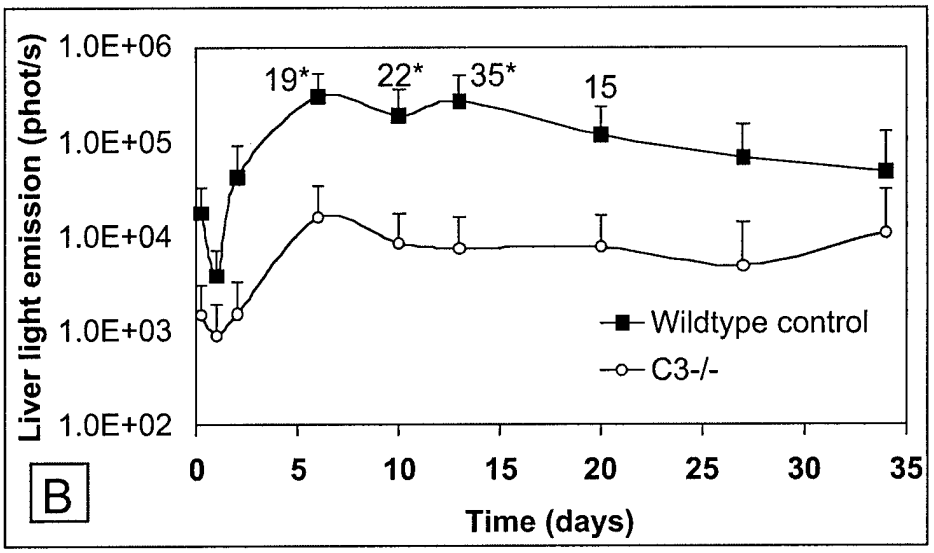
Wildtype control
C3-/-
0
5
10
15
20
25
30
35
Time (days)
A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1.0E+02
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Wildtype control
C3-/-
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5
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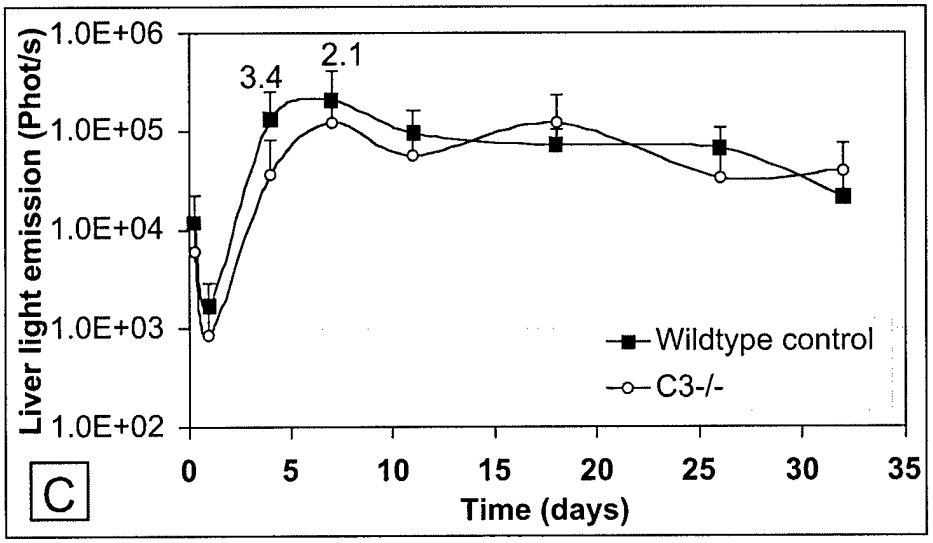
15
20
25
30
35
Time (days)
B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Wildtype control
C3-/-
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10
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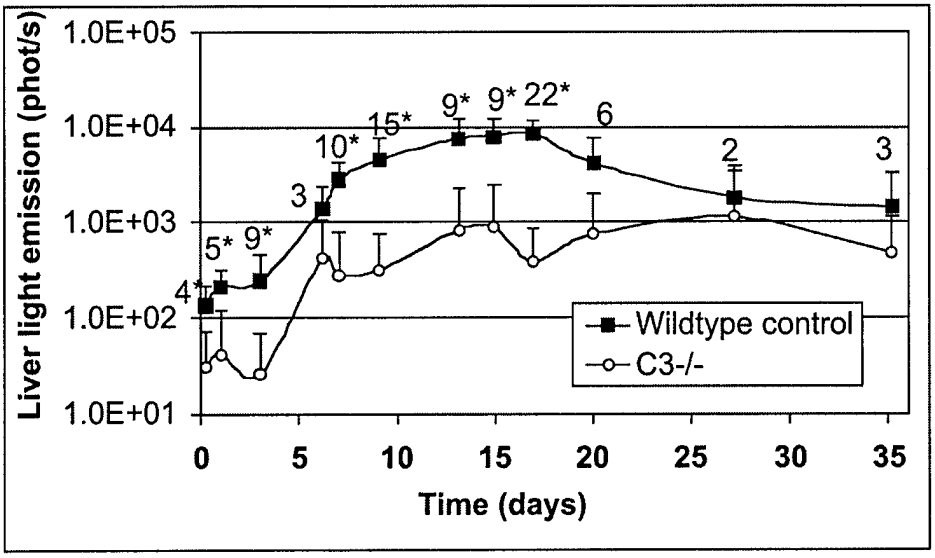
30
35
Time (days)
C

Figure 2


Liver light emission (phot/s)
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25
30
35
Time (days)
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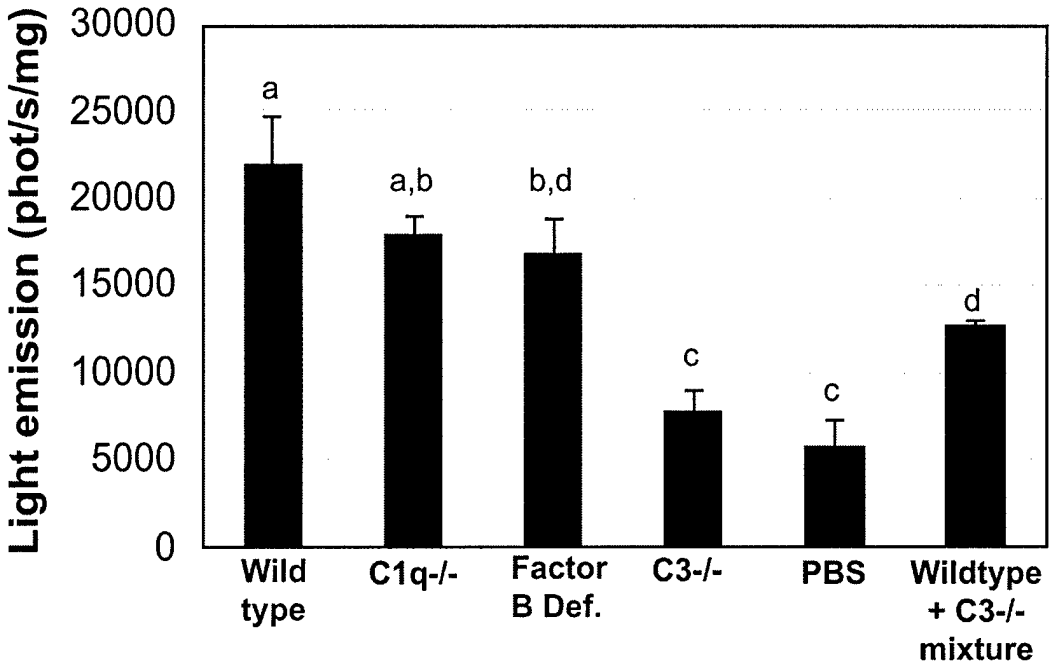
3
Wildtype control
C3-/-

Figure 3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25000
20000
15000
10000
5000
0
a
a,b
b,d
c
c
d
Wild type
C1q-/-
Factor B Def.
C3-/-
PBS
Wildtype + C3-/- mixture

Figure 4

CURRICULUM VITAE

Date: April 28, 2004

Tandra R. Chaudhuri
Citizenship: USA
Foreign Languages: Bengali, Sanskrit

RANK/TITLE: Associate Professor, Department of Radiology
Co-Director, Multi-Modality Imaging Center

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PROFESSIONAL CONSULTANTSHIPS:
Southeast Texas Radiation Oncology, Port Arthur, TX

EDUCATION:

George Washington University	MA	1970
University of Oklahoma	MS	1976
University of Calcutta	PhD	1983

LICENSURE: N/A

ACADEMIC APPOINTMENTS: (In reverse chronological order):

2000-present	Associate Professor Department of Radiology Co-Director, Laboratory for Multi-modality Imaging Assessment University of Alabama at Birmingham Birmingham, AL
1997-2000	Faculty Associate (UAB), Radiology - Molecular Imaging Development Lab
1995-2000	Director of Research/Consultant, Southeast Texas Radiation Oncology; Collaborator, Cancer Center of Port Arthur; Collaborator, University of Texas Health Science Center at San Antonio, Department of Nuclear Medicine; Collaborator (UAB), Radiology
1990-1995	Research Scientist (Associate Professor), University of Missouri

1985-1990	Research Assistant Professor, University of Missouri
1984-1985	Research Associate, Michael Reese Hospital and Medical Center, University of Chicago
1981-1984	Research Associate, University of Oklahoma
1979-1981	Post-Graduate Research Fellow, University of Calcutta
1976-1978	Research Associate, University of Texas Health Science Center at San Antonio

AWARDS/HONORS:

Graduate Scholarship	University of Oklahoma 1974-1976
Research Fellowship	University of Calcutta 1979-1981

PROFESSIONAL SOCIETIES:

American Society of Gene Therapy
Society of Nuclear Medicine
American Society for Microbiology
American Association of Tropical Medicine and Hygiene
American Association for the Advancement of Science
Sigma Xi Society

UNIVERSITY ACTIVITIES:

University of Missouri:

1. Established Cell Culture and Immunochemistry Laboratory Facilities for University Researchers.
2. Survey of P-32 and other radioisotopes for University Researchers.
3. Mentor, Summers 1992-94, Undergraduate summer interns in NSF funded program.

UAB:

1. Co-established the Molecular Imaging Laboratory and Multi-Modality Imaging Assessment in the Department of Radiology, 1995-Present.
2. Established the cell culture laboratory in the Department of Radiology.

MANUSCRIPT REVIEWER:

Journal of Immunology
Journal of Bacteriology

MAJOR RESEARCH INTERESTS:

1. Early detection and treatment of prostate, ovarian, breast, lung, pancreatic and other cancers by Multi-Modality Imaging.
2. Efficacy of novel anti-cancer/anti-inflammatory drugs by imaging with radiotracer molecules.
3. Molecular mechanism of rheumatoid arthritis.
4. Non-invasive screening and imaging for the early detection of prostate, ovarian, breast, cervical and other cancers.

GRANT SUPPORT:

1. Neutron Activation of Sm2O3 Tablets: Analyses and Clinical Studies, Investigators: PI: K Zinn, **TR Chaudhuri**, and S Morris; Procter and Gamble, $8,500; April 1993 - December 1994.

2. Production and Purification of High Specific Activity Cu-64 for Clinical Studies, Investigators: PI: K. Zinn, **TR Chaudhuri**, and S Morris; Washington University, $35,000; March 1993 - April 1995.

3. Nuclear Imaging of Adhesion Molecules in Inflammatory Disease. PI: KR Zinn, Co-Investigator: **TR Chaudhuri**. Agency: SNM Educ. & Research Foundation Type: Research grant. Period: 08/01/96 - 07/31/98, $50,000. Goal: To develop radiolabeled peptides for imaging the *in vivo* expression of E-Selectin.

4. Selective Transduction for Early Detection and Therapy of Cancer. PI: DT Curiel. Consultant: **TR Chaudhuri.** Agency: NCI. Type: Contract. Period: 10/1/99 - 09/30/02, $1,780,510. Goal: We propose the development of a novel system capable of selective transduction of target cells in the context of the clinical settings of: 1) post-treatment recurrent neoplastic disease and metastatic disease, and 2) early subclinical/undetected pre-neoplastic disease in susceptible cohorts.

5. Light based imaging for Breast Cancer. PI: **TR Chaudhuri.** Agency: UAB Cancer Center (Avon). Period**:** 9/1/2000 - 8/31/2002, $250,000. Goal: Non-invasive detection and treatment of breast cancer.

6. *In vivo* Light-based Imaging for Early Detection and Monitoring of Ovarian Cancer. Ovarian Spore (Specialized Program of Research Excellence - Spore). PI: **TR Chaudhuri**. 01/01/02-01/01/03. $50,000.

7. NCI, NIH. An *in vivo* Reporter System for Imaging Gene Transfer. PI: KR Zinn, Co-Investigator: **TR Chaudhuri.** Period: 7/6/1999 - 04/30/2004, $155,000/yr. Goal: To develop a Tc-99m-based reporter system for *in vivo* imaging of gene transfer and to conduct therapy studies using Re-188-peptides, in combination with bicistronic vectors encoding cytosine deaminase.

8. NIH. Specialized Program of Research Excellence (SPORE) in Ovarian Cancer. PI: E Partridge, Co-Investigator: **TR Chaudhuri.** Agency: NIH. Type: Contract. Period: 9/30/99 - 09/29/04. Total Direct~$100,000/year. Goal: **Dr. Zinn and Dr. Chaudhuri are directors on the *In vivo* Gamma-ray Imaging Core for Non-Invasive Imaging**.

9. Sankyo. Multi-modality Imaging Core, PPG, Overall PI, Koopman. PI: Zinn KR. Co-PI: **Chaudhuri TR**. Total Costs: $150,000 DC/year Total Period 10/01/01 - 09/30/04.

10. NCI, Infectivity Enhanced adenoviral vectors for ovarian cancer, total direct =$1,232,741. PI: Ronald D. Alvarez; Co-Investigator, **Chaudhuri TR** . Total Period 8/9/2001 - 8/8/2004.

11. NIH, Enhanced CRAd for esophageal adenocarcinoma, PI: Masato Yamamoto, Co-Investigator: (5%) **TR Chaudhuri**. Total Direct=$250,000/yr, total period 07/30/03-06/30/08.

12. HSF, Enhancement of the laboratory for multimodality imaging assessment. PI: Kurt R. Zinn, Co-Investigator: **TR Chaudhuri** Total=$450,000, Total Period 03/01/03 to 02/28/05. **(NEW).**

13. NIH, Career Development Award. Brain SPORE in molecular therapeutics for anaplastic glioma. PI: **TR Chaudhuri.** Total 65,250/year. Total Period: 06/01/03 to 05/31/05. Renewal for second year upon progress.

14. NIH. Breast SPORE. Co-Investigator: **TR Chaudhuri.** Total 50,000. Total Period: 10/01/03 to 09/30/04. Renewal for second year upon progress.

15. NIH grant. Comprehensive Cancer Center Core Support Grant. Instrument grants for small animal imaging equipment (Administrative Supplement). PI: AF LoBuglio. Co-Investigators: Zinn KR, **Chaudhuri TR**, Robbin ML. Total Costs: $170,000. Total Period: 9/1/03 to 3/31/04. **(NEW).**

16. Cystic Fibrosis Foundation. Cystic Fibrosis Gene Therapy Core Center, PPG, Overall PI, Sorscher: Development of Multimodality Approaches for Non-invasive Imaging of Rodent Lung. PI: **Chaudhuri TR**. Total Period: 05/01/03 - 04/30/04. Total Costs ~$50,000. **(NEW).**

17. NIH, SPORE in Pancreatic Cancer, PI: Vickers S, Co-Investigator: **TR Chaudhuri**, Imaging component of the animal models core. Period: 06/01/03 to 08/31/08, Total Costs: 650,000 direct/year ($40,000/year for imaging). **(NEW).** Renewal for second year upon progress.

18. NIH, Brain SPORE Developmental Project. PI: Wu, H. **Director/Mentor: Chaudhuri, TR.** Transcytosis-targeted adenoviral vector for brain cancer. Period: 01/01/2004 to 12/31/2004, Total Costs: $ 45,000. **(NEW)**. Renewal for second year upon progress.

19. NIH, Targeted Adenovirus Vectors for Gene Therapy of prostate cancer. PI: Victor Krasnykh, Co-Investigators, Kurt R. Zinn and **Tandra R. Chaudhuri**. Period: 07/01/03 to 06/30/08, $1,809,800 total costs. (funded and moved from UAB). **(NEW)**

20. DOD grant. Non-invasive Dual Modality Imaging for the Early Detection and Monitoring of Breast Cancer During Therapy. PI: **TR Chaudhuri**. Total Direct=$100,000/yr, 01/01/02 – 12/31/04.

21. NIH. Ovarian SPORE Developmental Project. Early detection of ovarian cancer by high frequency ultrasonography. PI: Zinn KR, Co-Investigator: **Chaudhuri, TR.** Total Costs: 50,000. Total Period: 01/30/04 to 01/29/05. Renewal for second year upon progress.

22. NIH. Ovarian SPORE Developmental Project. Exploring Human Gamma Delta T-cells for the Immunotherapy of Ovarian Cancer. PI: Lopez, Richard. Co-Investigator: **Chaudhuri, TR. (NEW).** Total Costs: 50,000. Total Period: 01/30/04 to 01/29/05. Renewal for second year upon progress.

GRANTS PENDING:

1. NIH, RO1 Competitive Continuation, Specialized Program of Research Excellence (SPORE) in Ovarian Cancer. PI: Edward Partridge; **TR Chaudhuri is Co-Investigator and Co-Director of Imaging Core** (10% effort), Total Direct ~ $7,000,000, 05/01/04-04/30/09. **(NEW)**.

2. NIH. Southern Molecular Imaging Link (SMIL). PI: Zinn KR. Co-Investigator: **Chaudhuri TR.** Total Period: 7/1/04 - 6/30/09. Total Costs: $899,730/5 years. **(NEW)**.

GRANTS IN PREPARATION:

1. Multi-Modality Imaging to Study the Molecular Mechanism of Bone Metastasis in Breast and Prostate Cancers. PI: **TR Chaudhuri.**

Research Support for Students at the University of Missouri:

1. Scientific Applications of Neutrons at a University Research Reactor, Investigators: F. Ross, S. Morris, K. Zinn, M. Glascock, J. Farmer, R. Berliner, G. G. Ehrhardt, A. Ketring, B. Yelon, **T. Chaudhuri**, H. Neff, and H. Kaiser, NSF; $165,000, 1992-1995.

Other: Invention Disclosures:

1. Disclosed (UAB): The human type 2 somatostatin gene in combination with a radiolabeled somatostatin-avid peptide functions as an *in vivo* reporter system for imaging gene transfer. Inventors: K Zinn, D Buchsbaum, B Rogers, **T R Chaudhuri**, March 1999.

2. Disclosed (UAB): An in vivo reporter system for imaging gene transfer, Inventor: K. Zinn, **T.R. Chaudhuri**. March 1999.

3. Disclosed (UAB): Novel Promoter/Reporter Screening System. K Zinn, **TR Chaudhuri**, B Rogers, October 1999.

4. Method for production of luciferase-positive cancer cell lines for imaging, K. Zinn, **T.R. Chaudhuri**, and S. Ponnazhagan. 1-21-03.

5. In vivo inflammation monitor. K. Zinn, **T.R. Chaudhuri**, M. Yamamoto. 2-7-03.

6. Disclosed (UAB): Application for Fluorescent Stereomicroscopic Imaging for the early detection and treatment monitoring in non-invasive way. **Chaudhuri, TR** , Zinn. KR.

Other: PATENTS granted and submitted

1. U.S. Provisional Application: Methods and Compositions for *in vivo* inflammation monitoring. Inventor: K. Zinn, **T. Chaudhuri.**

2. U.S. Submitted: Gene Transfer Imaging and Uses Thereof, Continuation, Inventors: D. Buchsbaum, K. Zinn, B. Rogers, **T. Chaudhuri**, D. Curiel.

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2. **Chaudhuri TR**, Zinn KR, McDonald GA, and Chaudhuri TK. Analysis of Human Monoclonal Antibody Against Ovarian Cancer. (presented at the Missouri Valley and Central Chapter meeting, Society of Nuclear Medicine, Oct 16-18, 1992, St. Louis, MO).

3. Zhihong Cao, Kurt R. Zinn, Amanda Stargel, Pushpa L Simhadri, Tong Zhou, Selvarangan Ponnazhagan, Albert F. LoBuglio, Donald J. Buchsbaum and **Tandra R. Chaudhuri**. Non-invasive imaging of non-palpable breast cancer xenografts during therapy. 2003 Annual Research Retreat. (presentation at the Comprehensive Cancer Center. October 2003 UAB). **Awarded for outstanding work in cancer research.**

4. **Chaudhuri TR**. Multi-modality Imaging of Metastasized Breast Tumors in Mice Brain. 2004 Inter Brain SPORE conference, Jan 22-23, UAB.

5. **Chaudhuri TR.** Efficacy of TRA-8 in breast cancer xenografts by bioluminiscent imaging. 2003 SANKYO's annual meeting. November, UAB.

INVITED LECTURES

1. Regional conference of American Society for Microbiology, University of Missouri, Columbia, MO, March, 1993. Title: Radioimmunodetection and radioimmunotherapy for ovarian and breast cancers. **Chaudhuri TR**.
2. International Isotope Society, 7th meeting of the U.S. Central Section, Oct. 7, 1994. Title: Review of Monoclonal Antibody Applications in Nuclear Medicine. **Chaudhuri TR**.
3. University of Calcutta, India. Oct. 1981. Title: Mechanism of gene transfer in gram negative bacteria. **Chaudhuri TR.**
4. Light-based and gamma camera imaging for the early detection and monitoring of ovarian cancer. July 2001, Wash. D.C. SPORE meeting. **Chaudhuri TR.**
5. **Chaudhuri, TR.** Invited Speaker. Academy of Molecular Imaging, March 2004, in Orlando, Florida.

TEACHING/SERVICE ACTIVITY: *In vivo* gamma-ray imaging core facility

ACADEMIC SERVICE:

1. Served as an Active member of Executive Committee of Ovarian SPORE for grant review.
2. Served as an Active member of Executive Committee of Brain SPORE for grant review.
3. Reviewed Breast SPORE grant.

TEACHING ACTIVITIES/FORMAL LECTURES (at UAB):
STUDENTS ADVISED AT THE UNIVERSITY OF MISSOURI:
UNDER GRADUATES

1. Brent Bell, Summer 1991 REU program, Project: Differential Solubility of Se-75-Labeled Proteins, Mentors: K. Zinn and **T. Chaudhuri**.
2. Maggie Stammeyer, Summer 1992 REU program, Project: A Procedure for the Study of Trace Element Binding to Proteins using High Specific Activity Cu-64. Mentors: K. Zinn and **T. Chaudhuri.**
3. Jeffery Johnson, Summer 1993 REU program, Project: Genetic Variation in Copper-binding Proteins in Rat Brain, Mentors: K. Zinn and **T. Chaudhuri**.
4. Jennifer Johnson, Summer 1993 REU program, Project: Purification of Monoclonal Antibody, Mentors: K. Zinn and **T. Chaudhuri.**

GRADUATE - MS DEGREE

1. Karalyn Littlefield, MS, 1990-1992, Development of nutrition and food science. Project: *In vitro* studies of anti-cancer drugs.

GRADUATE - PhD DEGREE

1. Joseph Temenak, PhD Department of Molecular Microbiology and Immunology, University of Missouri-Columbia. Project: Molecular immunology in infectious disease.
2. Lori Pellet, PhD Nutrition and food science

Technical and Professional Staff Trained and Other Students Assisted at Univ. of Missouri and at UAB:

1. Madeline Mason, Research Reactor, University of Missouri. Trained in cell culture and immunology research.
2. Wu Qi, UAB, Division of Nuclear Medicine. Trained in cell culture and *in vitro* experiments.
3. Zhu Min. UAB, Division of Nuclear Medicine. Trained in cell culture and *in vitro* experiments.
4. Gloria Robinson, Research Assistant, Trained in cell culture and *in vitro* research. Department of Radiology, UAB.
5. Ashley Davis, Department of Radiology, UAB, Trained in Molecular Imaging Research. Department of Radiology, UAB.
6. Zhihong Cao, MD, Department of Medicine, UAB. Research Associate.
7. Cristina Rodriguez-Burford, PhD, Research Associate. Dept of Radiology, UAB.
8. Amanda Stargel, Research Assistant. Department of Medicine, UAB.
9. Xiang Feng, MD, Research Associate. Department of Radiology, UAB.
10. Pushpa Simhadri, MS. Clinical Data Analyst. Department of Medicine, UAB.
11. Hongju Wu, PhD. Research Assistant Professor, Department of Radiology, UAB.
12. Glorisa Reason, MS, Research Technician. Department of Medicine, UAB.